# SUPPLEMENTARY FIGURES

*CPT: pharmacometrics & systems pharmacology*

# Prediction of gastric pH-mediated drug exposure using physiologically based pharmacokinetic modeling: A case study of itraconazole

Eunsol Yang, PhD[1,2], Kyung-Sang Yu, MD, PhD[1], SeungHwan Lee, MD, PhD[1]

[1] Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

[2] Kidney Research Institute, Seoul National University Medical Research Center, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

Correspondence: SeungHwan Lee

Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

E-mail: leejh413@snu.ac.kr

# TABLES OF CONTENTS

**SUPPLEMENTARY FIGURES** ..... 3

**Figure S1** Current Prospective Study design ..... 3

**Figure S2** PBPK model refinement 1 – Performance in the fasted state under normal gastric acidity ..... 4

**Figure S3** PBPK model refinement 2 – Performance for gastric pH-mediated exposure ..... 5

**Figure S4** 24-h gastric pH profiles in Current Prospective Study ..... 6

**Figure S5** Individual changes in pharmacokinetics in Current Prospective Study ..... 7

**Figure S6** Correlation between gastric pH and pharmacokinetics in Current Prospective Study ..... 8

**Figure S7** Impact of (a) gastric residence time, (b) initial volume of stomach fluid, and (c) gastric bile concentration on fraction absorbed ($f_a$) of itraconazole ..... 9

## SUPPLEMENTARY FIGURES

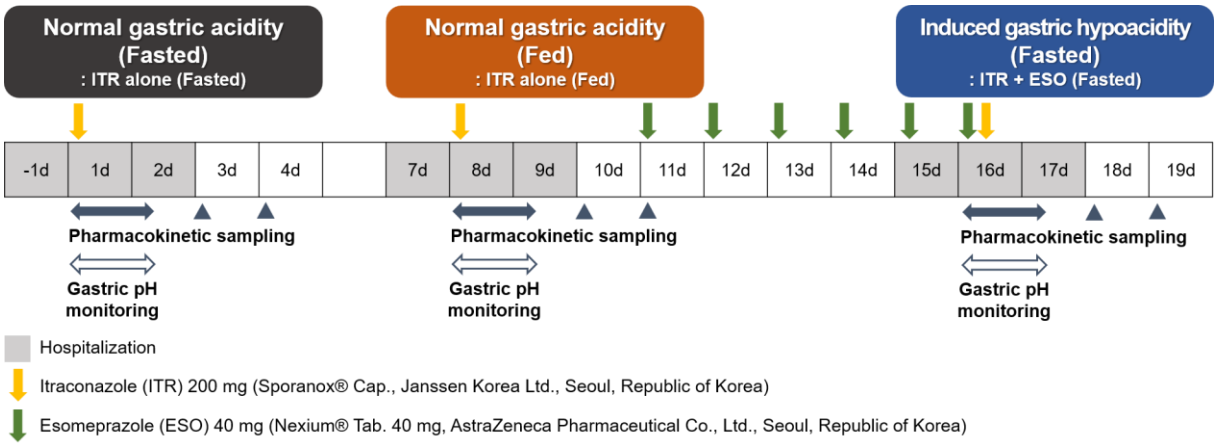


**Figure S1.** Current Prospective Study design

The fasted state means at least 10 hours of fasting before dosing, and the fed state means 30 minutes after intake of a high-fat meal, which contained 800 to 1000 calories with approximately 50% fat.

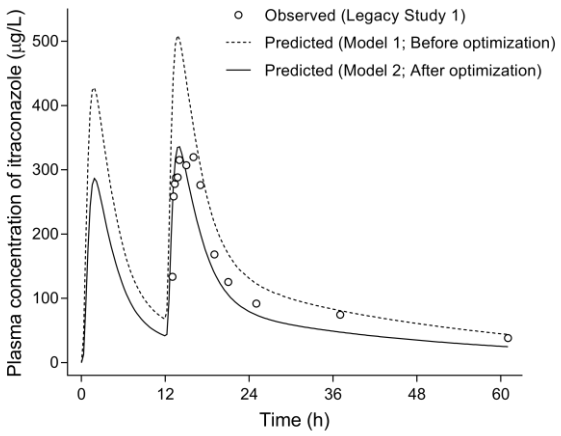


**Figure S2.** PBPK model refinement 1 – Performance in the fasted state under normal gastric acidity: Predicted plasma concentration-time profiles of itraconazole following a single oral administration of itraconazole 200 mg before and after optimization, along with the observed values in Legacy Study 1 (normal gastric acidity; fasted)

The dashed line denotes the predicted arithmetic mean concentration-time profile using the default values of DLM scalar, 1, and particle radius, 10 μM (i.e., Model 1; before optimization).

The solid line denotes the predicted arithmetic mean concentration-time profile using the values of DLM scalar and particle radius optimized by clinical data obtained from Legacy Study 1 (i.e., Model 2; after optimization).

The open circles denote the observed arithmetic mean concentrations obtained from Legacy Study 1.

PBPK, physiologically based pharmacokinetic; DLM, diffusion layer model

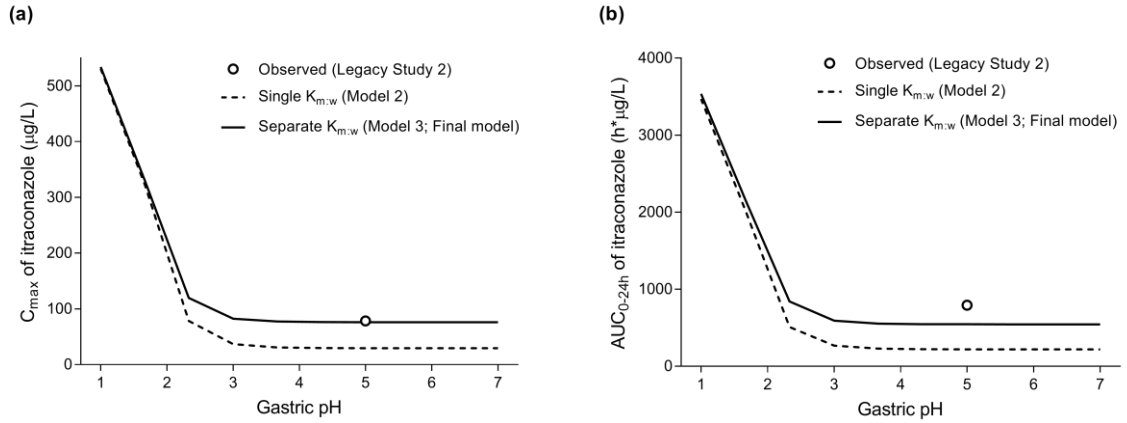


**Figure S3.** PBPK model refinement 2 – Performance for gastric pH-mediated exposure: Impact of gastric pH on (a) $C_{max}$ and (b) $AUC_{0\text{-}24h}$ of itraconazole in fasted condition

The dashed lines and solid lines denote the predicted impact using single $K_{m:w}$ values (i.e., Model 2) and separate $K_{m:w}$ values (i.e., Model 3; final model), respectively.

The open circles denote the observed values obtained from Legacy Study 2.

PBPK, physiologically based pharmacokinetic; $C_{max}$, maximum plasma concentration; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24h post-dose

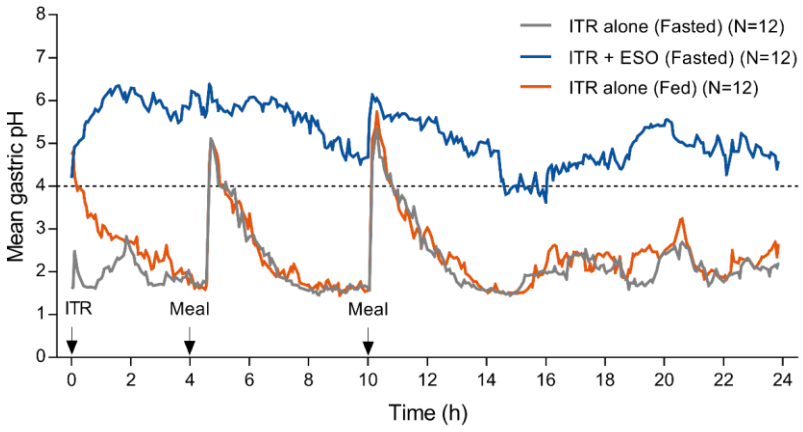


**Figure S4.** 24-h gastric pH profiles in Current Prospective Study: Arithmetic mean gastric pH-time profiles for 24 hours following a single oral administration of itraconazole 200 mg alone or with esomeprazole 40 mg in fasted condition, or alone in fed condition

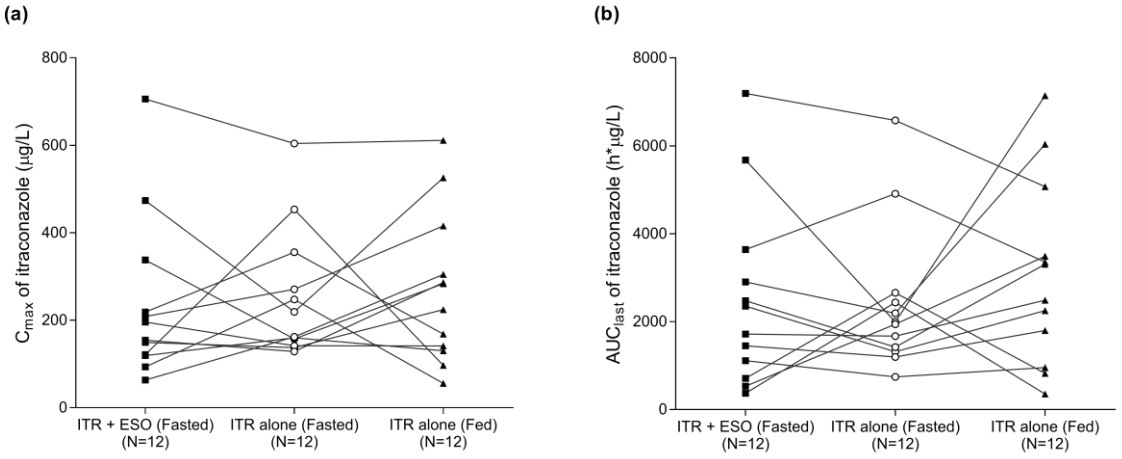


**Figure S5.** Individual changes in pharmacokinetics in Current Prospective Study: (a) $C_{max}$ and (b) $AUC_{last}$ of itraconazole following a single oral administration of itraconazole 200 mg alone or with esomeprazole 40 mg in fasted condition, or alone in fed condition

ITR, itraconazole; ESO, esomeprazole; $C_{max}$, maximum plasma concentration; $AUC_{last}$, area under the concentration-time curve from 0 to last measurable time point

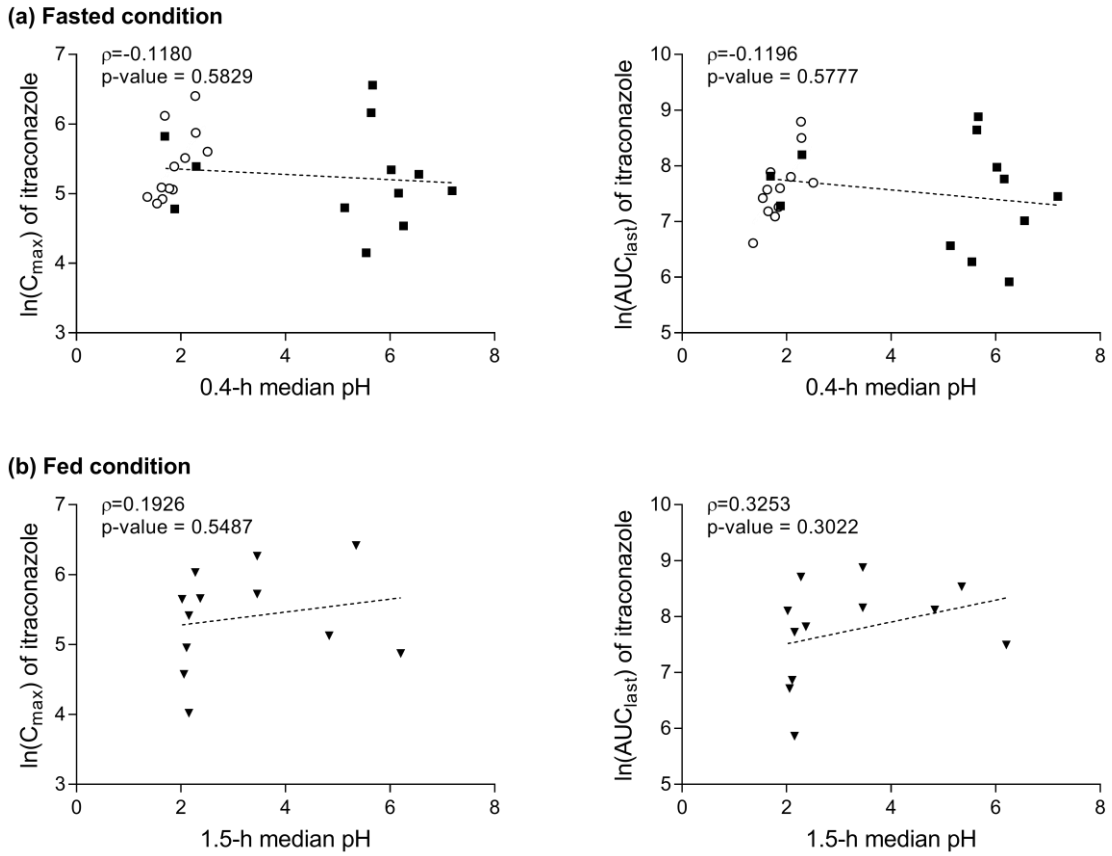


**Figure S6.** Correlation between gastric pH and pharmacokinetics in Current Prospective Study: $C_{max}$ (left panel) and $AUC_{last}$ (right panel) of itraconazole in relation to median gastric pH in (a) fasted and (b) fed conditions

The open circles and closed squares denote 'Itraconazole alone (Fasted)' and 'Itraconazole + Esomeprazole (Fasted)', respectively. The closed reversed triangles denote 'Itraconazole alone (Fed)'. The dotted lines denote the linear regressions of fasted and fed conditions, respectively.

$C_{max}$, maximum plasma concentration; $AUC_{last}$, area under the concentration-time curve from 0 to last measurable time point; ρ, pearson correlation coefficient

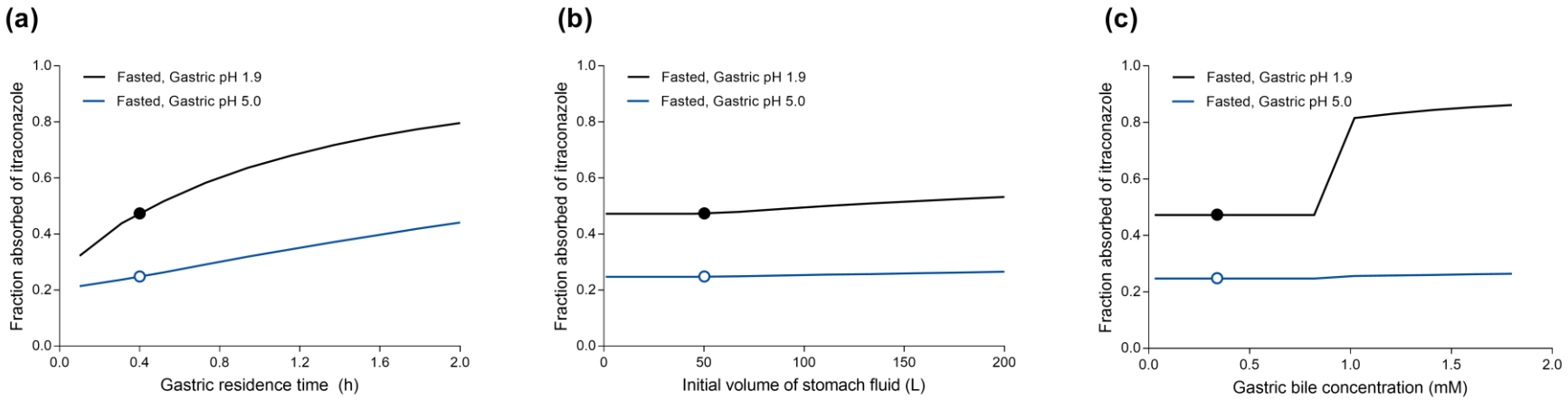


**Figure S7.** Impact of (a) gastric residence time, (b) initial volume of stomach fluid, and (c) gastric bile concentration on fraction absorbed ($f_a$) of itraconazole

The closed circles and open circles denote the values used for physiologically based pharmacokinetic (PBPK) simulation.